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HIV and Its Impact on the Infant Immune System

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Since the Human Immunodeficiency Virus was discovered in 1983, there have been about 60 million people infected worldwide, and over 4 million children have been infected under the age of 15. In 2003, there were about 5 million newly infected individuals, of which 700,000 were children under the age of 15. There are an estimated 40,000 new HIV infections per year,[?] and women consist of 47% of the HIV positive adults.[?] HIV continues to be a threat to the world population, in part because of its harmful effect on the immune system.

The HIV virus can bind to CD4$^+$ T cells because of chemical properties specific to those cells. Interaction of the virus with CD4$^+$ T cells allows the uncoating and the entry of the nucleocapsid into the cell, which contains the viral genome. HIV then uses reverse trancriptase to copy the two single strands of RNA into double-stranded DNA. This viral DNA then integrates into the DNA of the host cell, forever changing the properties of the particular cell. The virus remains inactive until the host cell is activated. Once the host cell is activated, the cell starts to reproduce copies of the viral RNA. New viral proteins assemble at the cell membrane and bud off to create new viruses. The process of budding off, in most cases, kills the host cell.[?] In other words, this process creates more virus particles, and at the same time destroys host cells of the immune system. Once the CD8$^+$ T cells are aware of the infection, they begin destroying actively infected cells. After a certain period of time, the CD4$^+$ T cell count begins to decline, leaving the immune system in a state of disorder. When CD4$^+$ T cells fall below a certain level, the immune system cannot recognize other pathogens entering the body, and opportunistic diseases normally end up defeating the immune system.

Although HIV is more prevalent in young adults, infants can also contract the virus from the infected mother. HIV is transmitted from a mother to her child in three different ways: during pregnancy (5% of total cases), childbirth (15% of total cases), and breastfeeding (10% of total cases). Overall, 25% of HIV- infected pregnant females pass on the disease to their infant. Studies have shown that children who were infected during pregnancy are more likely to progress faster to AIDS than children who were infected during childbirth or breastfeeding. Women are the fastest growing population of new HIV cases thus making more newborns vulnerable to the disease. However, the progression of HIV in infants has not been the focus for mathematical models.

There are numerous mathematical models which study the behavior of the HIV virus at a cellular level in an adult's immune system. These models[?,?] focus on the interaction of HIV and the immune system in adults Both models use a deterministic approach to help understand how HIV progresses in the human body.

In our model, we compare the invasion of HIV in an adult's immune system to an infant's immune system. In order to gain insight into the difference between systems, we rely on numerical simulations and analysis of the threshold parameter.

Let T_K denote the concentration of CD8$^+$ T cells, T_H denote the concentration of uninfected CD4$^+$ T cells, T_L denote the concentration of latently infected CD4$^+$ T cells, T_I denote the concentration of actively infected CD4$^+$ T cells, and V denote the concentration of free infectious virus particles. We have derived the following system of nonlinear ODE's to describe the dynamics of our model.

$$\begin{aligned}
\dot{T}_K &= s_1 - \mu_K T_K + r_K T_K \left(1 - \frac{T_K}{T_{Kmax}}\right) \\
\dot{T}_H &= s_2 - \mu_H T_H - kVT_H \ldots \\
&+ r_H T_H \left(1 - \frac{T_H + T_L + T_I}{T_{Hmax}}\right) \\
\dot{T}_L &= kVT_H - \mu_H T_L - aT_L \\
\dot{T}_I &= aT_L - \mu_I T_I - \delta T_I T_K \\
\dot{V} &= N\mu_H T_I - kVT_H - \mu_V V
\end{aligned}$$

Where s_1 represents the rate at which the thymus supplies CD8$^+$ T cells, s_2 represents the rate at which the thymus supplies CD4$^+$ T cells, r_K represents the Replication rate of CD8$^+$ T cells, r_H represents the replication rate of CD4$^+$ T cells, T_{Kmax} is the maximum number of CD8$^+$ T cells, T_{Hmax} is the maximum number of CD4$^+$ T cells, μ_K represents the natural death rate of CD8$^+$ T cells, μ_H represents the natural death rate of CD4$^+$ T cells, μ_V represents the natural death rate of virus cells, k represents the rate at which CD4$^+$ T cells become latently infected, a represents the rate at which latently infected CD4$^+$ T cells become actively infected, N is the average number of free virus produced by the death CD4$^+$ T cells, and δ represents the rate at which CD8$^+$ T cells kill the actively infected CD4$^+$ T cells.

The *virus free* steady state occurs at $V^* = T_L^* = T_I^* = 0$ where $T_K^* > 0$, and $T_H^* > 0$. Also, there is an *endemically infected* steady state when $V > 0$. The stability of these steady states was analyzed through linearization and the Routh-Hurwitz criteria.

It was determined that the virus free steady state is locally asymptotically stable when

$$N < \frac{(a+\mu_H)(\mu_V + kT_H^*)(\mu_H + \delta T_K^*)}{a\mu_H kT_H^*} = N_{crit} \tag{1}$$

For $N < Ncrit$, there exists only one steady state in the nonnegative orthant and, through the method of Lyapunov, we have shown that is globally stable when

$$N < \frac{\mu_H}{a} + 1$$

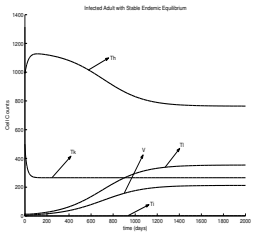
At $N = Ncrit$, the virus free steady state and the infected steady state coincide. Furthermore, there is a transcritical bifurcation at $N = Ncrit$, and the infected state emerges when $N > N_{crit}$ as a new steady state in $\mathbb{R}^5_+$. We find that, for certain parameter regimes, all the eigenvalues of the Jacobian Matrix of our system evaluated at the infected steady state have negative real part, which implies that the steady state is stable. However, there are certain parameter regimes where the infected steady state is unstable.

Next, a local sensitivity analysis was performed on the parameters relevant to the critical number of viruses produced by each dying CD4$^+$ T cell, that is, a, $\mu_{h,k}$, μ_v, k, δ, $r_{h,k}$, and $T_{hmax,kmax}$. The parameter with the sensitivity index of the greatest magnitude is the most effective in increasing N_{crit} when parameters are varied locally, where the sensitivity index is given by

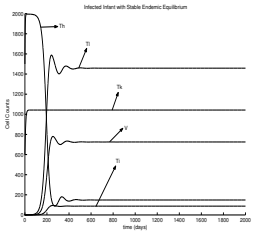
$$S = \frac{\lambda}{N_{crit}} \frac{\partial N_{crit}}{\partial \lambda}$$

where λ represents a parameter. For our model we take into consideration two critical values for N, one calculated for infants and one calculated for adults. In other words, we calculate one N_{crit} using parameter values for infants and another using parameter values for adults.It was found that for infants the greatest sensitivity index is obtained by the parameter δ. In biological terms, this implies that by increasing the rate at which CD8$^+$ T cells kill off the infected CD4$^+$ T cells, N_{crit} will increase most efficiently compared to changes in other parameters. In adults, increasing the death rate of the virus μ_v most effectively increases N_{crit} compared to the other parameters.[?]

Numerical simulations with our model demonstrate that the loss of CD4$^+$ T cells can take place on a time scale of years, as is characteristic of CD4$^+$ T cells dynamics in a person affected with HIV. From the numerical simulations, it can be seen that the depletion of CD4$^+$ T cells in an infant occurs much more rapidly in infants compared to adults, which is consistent with our current knowledge of HIV.



Stable Endemic for Adults



Stable Endemic for Infants

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